## REMARKS

Claims 86-89, 91-98, and 100-101 are pending and under examination (claim 99 having been canceled by the present amendment). Claim 90 is withdrawn from consideration as being drawn to a nonelected invention. Claims 86, 87, 91, 92, 96-98, 100 and 101 have been amended. The amendments to the claims are supported by the specification as filed at, *e.g.*, page 9, lines 23-28, and page 32, lines 23-30. No new matter has been added.

***Rejections under 35 U.S.C. § 112, second paragraph***

The Examiner rejects claims 93-95 and 98-100 "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". Applicants respectfully disagree and traverse the rejection.

Specifically, the Examiner states, at page 2 of the Office Action, that

> [c]laims 93-95 are indefinite in the recitation "than not administered in combination with said second composition. Claims 93-95 depend from claims 87-90 which claim the combination of both antagonist and a second composition, it is unclear how the antagonist would be administered in the absent [*sic.*] of the second composition since the base claims require a combination therapy.

At the outset, Applicants note that claims 87-90 do not recite an "antagonist". The Examiner is correct in pointing out that claims 93-95, because of the limitations of the base claims, require that the antibody be administered in conjunction with the chemotherapeutic agent. 93-95 merely recite the dosages of the compositions, when administered *in combination*, relative to dosages of the compositions when administered *individually*. The amount of the antibody or the chemotherapeutic agent is less than would be given if one of were treated with the antibody or chemotherapeutic agent alone. As such, claims 93-95 are not indefinite, and this rejection should be withdrawn.

The Examiner rejects claims 98-100 as indefinite "because '21.6' are [*sic.*] merely a laboratory designation which does not clearly define the claimed product" (Office Action at page 2). Claims 98 and 100, as amended, no longer recite "21.6", and claim 99 has been canceled, rendering this rejection moot.

***Rejections under 35 U.S.C. § 112, first paragraph -- Enablement***

The Examiner rejects claims 86-89 and 91-101 "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention" (Office Action at page 3). Specifically, the Examiner states that "[i]t appears that the '21.6' antibodies are essential to practice the claimed invention. However the specification fails to teach how to make the specific antibodies" (Office Action at page 3). Although Applicants disagree, in the interest of advancing prosecution, Applicants have amended claims 98 and 100 to remove reference to "21.6". Claim 99 has been canceled. Thus, this ground for rejection is now moot.

The Examiner also states that "the specification does not provide sufficient guidance and direction as how to make and use any 'antibody homolog' of anti-VLA-4" (Office Action at page 5). Although Applicants disagree, the claims have been amended to remove reference to "antibody homolog", rendering this ground for rejection moot.

The Examiner also rejects the claims for reciting the phrase "prophylactically effective". The claims have been amended to remove "prophylactically effective", thus overcoming this rejection.

In another aspect of the rejection, the Examiner states, at page 5 of the Office Action, that

> [w]hile the specification on page 37, line 4-12 discloses that B epitope-specific antibodies as [*sic.*] antibodies which can bind to VLA-4 at a site involved in ligand recognition and block VCAM-1 and fibronectin binding, however, the specification lacks guidance of the structure or what part of the VLA-4 involved in the ligand recognition and block VCAM-1 and fibronectin binding. The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only the antibodies against α4 and a melphalan, a bisphosponate [*sic.*], thalidomide and erythropoiention [*sic.*] as chemotherapeutic agent. A person of skill in the art is not enabled to make and use "an antagonist" and "a compound" as recited in the claims.[1] A person of skill in the art would not know which antagonists or compounds are essential to treat MM. Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies such "B epitope" for α4 (emphasis added).

[1] Applicants note that the terms "antagonist" and "compound" do not appear in the pending claims, contrary to the Examiner's assertion.

Applicants respectfully disagree. Numerous B epitope specific anti-VLA-4 antibodies are known in the art (*see, e.g.*, Pulido *et al.*, *J. Biol. Chem.* 266:10241-10245, 1991, a copy of which is enclosed). It is also clear from the art how to make a B epitope specific anti-VLA-4 antibody. Either of these known facts would enable the invention. Knowing the amino acid sequence or the molecular weight of the epitope is not needed to practice the invention. One simply need not know the sequence or molecular weight to administer an antibody to a human or even to make the antibody. This is discussed in more detail below.

The claimed invention is a method, namely a method for treating multiple myeloma comprising administering a combination of an anti-VLA-4 antibody, or an antigen-binding fragment thereof, and a chemotherapeutic agent. Enablement under 35 U.S.C. § 112, first paragraph, requires that "the specification describe how to make and how to use the invention. The invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application or patent" (MPEP § 2164, emphasis added). The pending claims recite methods for treating multiple myeloma using an anti-VLA-4 antibody and a chemotherapeutic agent. Claims 97 and 101 define the anti-VLA-4 antibody as a B epitope specific anti-VLA-4 antibody. Prior to the earliest priority date, B epitope specific anti-VLA-4 antibodies were known in the art. As described in the specification at page 37, lines 9-12 (emphasis added):

> Anti VLA-4 antibodies that will recognize the VLA-4 α4 chain epitopes involved in binding to VCAM-1 and fibronectin ligands (i.e., antibodies which can bind to VLA-4 at a site involved in ligand recognition and block VCAM-1 and fibronectin binding) are preferred. Such antibodies have been defined as B epitope-specific antibodies (B1 or B2) (Pulido et al., 1991, supra) and are also anti-VLA-4 antibodies according to the present invention.

Applicants are not claiming the B epitope specific anti-VLA-4 antibodies themselves (which were well known in the art at the time of filing), but are claiming methods of using them. The specification describes methods of making anti-VLA-4 antibodies (*e.g.*, at page 34, line 24, to page 36, line 26) and also teaches how to use the antibodies (*e.g.*, at page 49, line 30, to page 55, line 14). Thus, one of skill in the art, reading the specification, would know how to

make and use the claimed invention. As such, Applicants respectfully request this rejection be withdrawn.

***Rejections under 35 U.S.C. § 112, first paragraph – Written Description***

The Examiner rejects claims 86-89 and 91-101 "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (Office Action at page 7). Specifically, the Examiner asserts that

> [n]either the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (antibody homolog) to describe the claimed genus, nor does it provide a description of structural features that are common to species (B epitope). The specification provides no structural description of B epitopes or antibody homolog other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed B epitope and the antibody homolog looks like. The specification's disclosure is inadequate to describe the claimed genus of antibody homolog (Office Action at page 8).

Applicants respectfully disagree.

The Examiner concedes that "Applicant is in possession of a method of treating multiple myeloma comprising an anti-VLA-4 antibody and melphalan" (Office Action at page 7). However, the Examiner appears to reject the claims as reciting two genuses: the genus of "antibody homologs" and the genus of "B epitope" specific antibodies. The rejection has been met, in part, by amending the claims to remove reference to "antibody homolog". However, Applicants traverse the part of this rejection directed to "B epitope" specific antibodies below.

B epitope antibodies

Regarding the genus of "B epitope" antibodies, the Examiner states that the specification does not "provide a description of structural features that are common to [the] species" (Office Action at page 8). Applicants disagree.

According to the Guidelines, "the 'essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed" (Guidelines at page 1104). The Guidelines also state that

> [w]hat is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met (at page 1106, emphasis added).

Claims 97 and 101 limit the anti-VLA-4 antibodies used in the claimed methods to those that are "B epitope specific". The identifying characteristic provided by Applicants for the antibodies in claims 97 and 101 is the name of a particular epitope recognized by particular anti-VLA-4 antibodies (*i.e.*, a B epitope). As discussed above, B epitope specific antibodies were well known in the art at the time of filing. Given the fact that these antibodies were already known in the art, the application, by naming the B epitope, is sufficient in that it clearly conveys what was invented--the "essential goal" of the written description requirement. To point to the epitope by name, when the epitope is structurally and physically characterized in the art, says "use this specific structurally characterized art-known element." The degree of detail needed to convey the realization that the inventor was in possession depends on the essential character of the invention and the level of skill and knowledge in the art. If the art were devoid of information as to B epitope specific anti-VLA-4 antibodies, a great level of detail would of course be called for. However, in this case the level of knowledge and skill in the art is considerable and naming of the known element is sufficient to satisfy the written description requirements.

Further, Example 16 of the Revised Interim Written Description Guidelines Training Materials (hereafter "Training Materials") discuss the adequacy of written description for antibodies. In Example 16 of the Training Materials (at page 59, emphasis added),

> The specification teaches that antigen X has been isolated and is useful for detection of HIV infections. The specification teaches antigen X as purified by gel filtration and provides characterization of the antigen as having a molecular weight of 55 KD. The specification also provides a clear protocol by which

> antigen X was isolated. The specification contemplates but does not teach in an example antibodies which specifically bind to antigen X and asserts that these antibodies can be used in immunoassays to detect HIV. The general knowledge in the art is such that antibodies are structurally well characterized.... It is also well known that antibodies can be made against virtually any protein.

In concluding that the specification provides adequate written description for the claimed antibodies, the Training Materials state (at pages 59-60, emphasis added):

> Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X.

The Examiner acknowledges that Applicants are in possession of a method of treating multiple myeloma using an anti-VLA-4 antibody and melphalan. According to the Training Materials, the level of skill and knowledge is high in the art of antibodies. Given the high level of skill and knowledge in the art of antibodies, one of skill in the art would recognize that Applicants were in possession of the use of anti-VLA-4 antibodies that bind to a specific epitope (*i.e.*, B epitope), especially given that such antibodies were known in the art at the time of filing. Thus, the specification provides adequate written support for the claimed invention, and Applicants respectfully request this rejection be withdrawn.

***Rejections under 35 U.S.C. § 103(a)***

Claims 86-89 and 91-101 are rejected as unpatentable over Van Zaanen *et al.*, *Br. J. Haematol.* 102:783-790, 1998 ("Van Zaanen") in view of Masellis-Smith *et al.*, *Cancer Res.* 57:930-936, 1997 ("Masellis-Smith") and Lokhorst *et al.*, *Blood* 84:2269-2277, 1994 ("Lokhorst") and U.S. Patent No. 5,885,786 ("Cabot") or Alexanian *et al.*, *J. Am. Med. Assoc.* 208:1680-1685, 1969 ("Alexanian") and Owens *et al.*, *J. Immunol. Methods* 168:149-165, 1994 ("Owens") or U.S. Patent No. 5,840,299 ("Bendig"). Claims 86-89 and 91-101 are alternatively rejected as unpatentable over U.S. Patent No. 6,495,525 ("Lee") in view of

Kamata *et al.*, *Biochem. J.* 305:945-951, 1995 ("Kamata") and Cabot or Alexanian and Owens or Bendig. This rejection is respectfully traversed.

At the outset, Applicants disagree with the Examiner's determination that "the filing date for the limitation B epitope is deemed to be the filing date of the instant application" (Office Action at page 8). The international application PCT/US99/21170 (published as WO 00/15247), to which the present application claims priority, discloses B epitope specific anti-VLA-4 antibodies (*see, e.g.*, page 19, lines 13-15 of the published application). Thus, this limitation is entitled to the filing date of at least the PCT application.

Applicants also disagree with the Examiner's statement that "the parent application is drawn only to the administration of anti-α4 antibody" (Office Action at page 8).

I. Van Zaanen in view of Masellis-Smith and Lokhorst and Cabot or Alexanian

Claims 86-89, 91, 93-97 and 101 are rejected as unpatentable over Van Zaanen in view of Masellis-Smith and Lokhorst and Cabot or Alexanian. The rejection is respectfully traversed.

Van Zaanen teaches the use of an anti-IL6 antibody in the treatment of MM. Masellis-Smith and Lokhorst teach the use of anti-VLA-4 antibodies in various *in vitro* assays, but do not teach or suggest the use of anti-VLA-4 antibodies to treat MM. Further, none of these references teaches or suggests the use of an anti-VLA-4 antibody in combination with a chemotherapeutic agent, much less the specific combinations (e.g., an anti-VLA-4 antibody with melphalan) in the treatment of MM. Cabot teaches the use of melphalan to treat MM. Alexanian teaches the use of melphalan in combination with prednisone (a non-biologic, non-antibody drug) to treat MM. Neither Cabot nor Alexanian, alone or in combination, teaches or suggests the use of a chemotherapeutic agent, *e.g.*, melphalan, in combination with an anti-VLA-4 antibody (a biologic) to treat MM, as recited in the claims.

There is a well-established legal standard for obviousness: there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; there must be a reasonable expectation of success; and the prior art reference must teach or suggest all the claim limitations. Moreover, the suggestion to make the claimed

combination and the expectation of success must both be found in the prior art, not in Applicants' disclosure. MPEP at 2143, citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

As discussed above, claims 86-89, 91, 93-97 and 101 are directed to the treatment of multiple myeloma (MM) with anti-VLA-4 antibodies in combination with a chemotherapeutic agent. The Examiner has not made a *prima facie* case for obviousness.

There is no suggestion or motivation in the art argued by the Examiner to combine an anti-VLA-4 antibody with a chemotherapeutic agent to treat MM, and much less the specific combinations, e.g., an anti-VLA-4 antibody and melphalan. Although Alexanian teaches the treatment of MM using a combination of melphalan and prednisone (a steroid), Alexanian does not teach or suggest the use of an anti-VLA-4 antibody (a biologic) in combination with a chemotherapeutic agent. Steroids and biologics are completely different agents, and Alexanian does not provide any teaching or suggestion to one of skill in the art to substitute a biologic (an anti-VLA-4 antibody) for the steroid (prednisone) disclosed in Alexanian.

For these reasons, the Examiner has not made out a *prima facie* case for obviousness, and Applicants respectfully request this rejection be withdrawn.

Claim 92 is rejected as unpatentable over Van Zaanen in view of Masellis-Smith and Lokhorst and Cabot or Alexanian and Owens. Claims 98-100 are rejected as unpatentable over Van Zaanen in view of Masellis-Smith and Lokhorst and Cabot or Alexanian and Bendig. As discussed above, Van Zaanen, Masellis-Smith, Lokhorst, Cabot and Alexanian do not teach or suggest the invention as claimed, and neither Owens nor Bendig makes up for the deficiencies of the cited references. Thus, Applicants respectfully request this rejection be withdrawn.

Unexpected or surprising results

Even if a *prima facie* case of obviousness for these claims had been made (which Applicants do not concede), Applicants' surprising results would rebut the *prima facie* case.

The claims are directed to the use of anti-VLA-4 antibodies in combination with a chemotherapeutic agent. When a combination of distinct treatments is administered to a patient, the combination cannot be expected necessarily to improve the results of either treatment alone. One can see a number of outcomes. For example, two therapeutic agents may act on the same

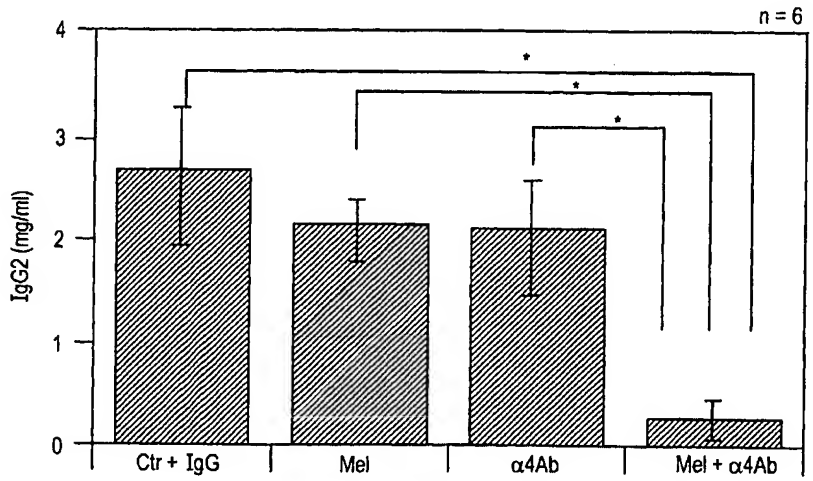
target, such that the two agents compete with each other to modulate the same pathway. The two agents may interact with each other, for example, to form inactive heterodimers. One agent may positively modulate a favorable pathway while the second agent may positively modulate an undesired pathway, leading to antagonistic effects. These are only a few examples of possibilities. Given the number of possible outcomes, however, one cannot predict *a priori* whether a combination of two treatments will be beneficial or synergistic. However, Applicants have demonstrated that the combination of an anti-VLA-4 antibody and a chemotherapeutic agent produced surprisingly effective results in animal models of MM, compared to treatment with the antibody or chemotherapeutic agent alone.

As described on page 72, lines 6-18 of the specification (emphasis added):

> In one particular set of experiments on the combined effects of melphalan and anti-alpha 4 integrin Ab in 5TGM1 model, as shown in an experimental protocol in Figure 7, an initial high dose of 200 μg mAb was given during the first week, followed by a maintenance dose of 100 μg. Melphalan was given three times. Animals (scid/nu/bg mice) were sacrificed at day 28 and serum IgG2b levels (a surrogate marker of tumor burden) and tumor burden in bone were measured (histomorphometric analysis of bones). The serum IgG2b was only modestly affected by either melphalan or anti-α4 mAb, while the combination produced a significant drop in IgG2b levels (Fig. 8).

For the Examiner's convenience, Figure 8 from the specification is reproduced below:

*FIG. 8*



Applicants note that IgG2b is indicative of tumor burden. As the graph demonstrates, treatment with the antibody alone reduced IgG2b levels (from about 2.7 mg/ml to about 2 mg/ml), and treatment with melphalan alone reduced IgG2b levels (from about 2.7 mg/ml to about 2 mg/ml). However, treatment with the combination of antibody and melphalan resulted in a much more significant decrease in IgG2b levels (from about 2.7 mg/ml to about 0.3 mg/ml). The results seen with the combination are much more than simply an additive effect of treatments with the antibody and melphalan alone. In fact, these results demonstrate that treatment with the antibody and melphalan in combination are synergistic, compared to treatment with either agent alone.

One of skill in the art would not have predicted, at the time of filing, that an anti-VLA-4 antibody (a biologic) and melphalan (a derivative of nitrogen mustard) would be beneficial in combination, much less synergistic. Thus, Applicants' method of combination therapy produces surprisingly effective results over antibody monotherapy or melphalan monotherapy. Given the surprising results achieved with Applicants' claimed methods, any potential *prima facie* case of obviousness has been overcome. Accordingly, Applicants respectfully request that the rejection be withdrawn.

II. Lee in view of Kamata and Cabot or Alexanian

Claims 86-89, 91, 93-97 and 101 are is rejected as unpatentable over Lee in view of Kamata and Cabot or Alexanian. The rejection is respectfully traversed.

Claims 86-89, 91, 93-97 and 101 are directed to the treatment of multiple myeloma (MM) with anti-VLA-4 antibodies in combination with a chemotherapeutic agent.

Lee discloses the use of a small molecule VLA-4 inhibitor (oMePUPA-V) to treat animal models of pulmonary inflammation (airway hypersensitivity) and delayed type hypersensitivity. Lee suggests that the small molecule inhibitor could also be used to treat "VLA-4-mediated cell adhesion and pathologies associated with that adhesion, such as inflammation and immune reactions" and lists 20 specific disorders within that class. Kamata discloses various anti-VLA-4 antibodies but does not teach or suggest the use of anti-VLA-4 antibodies for the treatment of MM. Further, neither Lee nor Kamata teaches or suggests the use of an anti-VLA-4 antibody in combination with a chemotherapeutic agent in the treatment of MM. Cabot teaches the use of

melphalan to treat MM. Alexanian teaches the use of melphalan in combination with prednisone (a non-biologic) to treat MM. Neither Cabot nor Alexanian, alone or in combination, teaches or suggests the use of a chemotherapeutic agent, *e.g.*, melphalan, in combination with an anti-VLA-4 antibody (a biologic) to treat MM, as recited in the claims.

The Examiner argues that one of ordinary skill in the art would have been motivated to substitute the anti-VLA-4 antibodies disclosed by Kamata for oMePUPA-V as disclosed in Lee to treat multiple myeloma because "the compounds of the invention are inhibitors of VLA-4 integrin thereby blocking the binding of VLA-4 to its various ligand, such as VCAM-1 and regions of fibronectin such is [*sic.*] antibodies to VLA-4" (Office Action at page 15). This rejection is respectfully traversed.

First, contrary to the Examiner's assertions, oMePUPA-V is simply not interchangeable with anti-α4 integrin antibodies. Although Lee teaches that oMePUPA-V has a broad range of therapeutic applicability, there is simply no indication in Lee or in any other reference cited that an antibody inhibitor of α4 integrins, as recited in the claims (rather than a small molecule inhibitor), would have the same applicability for treating MM. Contrary to the Examiner's argument, a skilled artisan would simply not be motivated to substitute an antibody disclosed in Kamata for the small molecule drug of Lee to treat MM.

Antibodies are completely different than small molecules. First, antibodies as a class of agent are vastly different in size than small molecule drugs such as oMePUPA-V. Due to its small size, a small molecule drug is typically directed to a "pocket" or specific docking site on the target molecule, where it may act as either an agonist or an antagonist. In contrast, antibodies are large molecules that, although they bind to a particular epitope, effectively cover a large surface area and thereby act to block a biological pathway though stearic hindrance, as opposed to binding a specific active site or pocket. For this reason alone, a skilled practitioner would not have believed oMePUPA-V to be interchangeable with an anti-VLA-4 antibody to treat MM in the claimed combination methods.

Second, in contrast to oMePUPA-V, an antibody-based therapeutic would be expected to implicate aspects of the immune response in its effect. The binding of Fc receptors by the Fc domain of an antibody molecule provides signals that activate and recruit immune and inflammatory cells, or, alternatively, that send inhibitory signals that downregulate immunity.

The implication of additional immune mechanisms with an antibody could result in a completely different effect in vivo than that of oMePUPA-V. Thus, a skilled artisan would not have reasonably predicted that an anti-VLA-4 antibody would have the same effect as oMePUPA-V *in vivo* in treating MM. Such antibody-specific mechanisms are an important reason why an antibody and a small molecule would not be considered interchangeable in treating MM.

Third, anti-VLA-4 antibodies, as recited in the claims, have a different specificity than oMePUPA-V. Lee teaches that oMePUPA-V is highly specific for VLA-4 (having α4/β1 subunits) but does not act on α4/β7 integrin (*see* Lee, page 7, lines 39-42 and page 25, lines 33-34). In contrast, the anti-VLA-4 antibodies recited in the claims can bind both α4/β1 and α4/β7, implicating an additional integrin pathway. The broader specificity of an anti-α4 integrin, compared to oMePUPA-V, would have made it unpredictable that an anti-α4 antibody would have the same effect as oMePUPA-V in treating MM.

Moreover, Applicants note that Lee discloses experiments that use oMePUPA-V to treat animal models of pulmonary inflammation (airway hypersensitivity) and delayed type hypersensitivity (*see* Lee, Examples 2-4). Lee lists a broad range of other immune and inflammatory diseases that can be treated with oMePUPA-V and also lists multiple myeloma and tumor metastasis. Multiple myeloma is a type of cancer (neoplasm) that develops in a subset of white blood cells but it is not an immune or inflammatory disorder *per se*, unlike the other disorders listed in Lee or the disorders treated in the *in vivo* examples in Lee. There is absolutely no motivation to select multiple myeloma from this long list in Lee to treat with an antibody. A skilled artisan would certainly not be motivated to use an antibody therapeutic to treat a neoplasm based on Lee's data showing that a small molecule drug against a target can be used to treat a disorder related to inflammation, or more particularly, to a hypersensitivity-type inflammatory response. Treating neoplasms with antibodies is a completely different area of medicine than treating immune- or inflammatory-mediated diseases with small molecule drugs.

Finally, Lee specifically teaches that an anti-VLA-4 antibody and oMePUPA-V are not interchangeable to treat inflammatory-mediated diseases. In Example 3, Lee compared the use of an anti-VLA-4 antibody to the use of oMePUPA-V to treat animal models of delayed type hypersensitivity. In this example, the antibody was effective, but the small molecule was not.

Thus, Lee does not teach or suggest the use of an anti-VLA-4 antibody in place of the small molecule oMePUPA-V.

In conclusion, a skilled artisan would find absolutely no motivation in the combination of the cited references to use an anti-VLA-4 antibody to treat multiple myeloma. Further, there is no suggestion or motivation in the cited references to combine an anti-VLA-4 antibody with a chemotherapeutic agent to treat MM, as recited in the pending claims. As such, the Examiner has not made out a *prima facie* case for obviousness. Accordingly, Applicants request that the rejection be withdrawn.

Claim 92 is rejected as unpatentable over Lee in view of Kamata and Cabot or Alexanian and Owens. Claims 98-101 are rejected as unpatentable over Lee in view of Kamata and Cabot or Alexanian and Bendig. As discussed above, Lee, Kamata, Cabot and Alexanian do not teach or suggest the invention as claimed, and neither Owens nor Bendig makes up for the deficiencies of the cited references. Thus, Applicants respectfully request this rejection be withdrawn.

Unexpected or surprising results

Even if a *prima facie* case of obviousness for these claims had been made (which Applicants do not concede), Applicants' surprising results, discussed above, would rebut the *prima facie* case. Accordingly, Applicants request that the rejection be withdrawn.

***Rejections under Judicially Created Doctrine of Obviousness-type Double Patenting***

Claims 86-89, 91, 93-96 and 101 are provisionally rejected as unpatentable over claims 12-16 of copending USSN 09/943,659. Once the present claims are deemed otherwise allowable, Applicants will address this rejection by submitting an appropriate terminal disclaimer by the common Assignees of the present application and the patent issuing from USSN 09/943,659. A terminal disclaimer is not an admission or comment regarding the merits of the rejection (Quad Envtl. Techs. Corp. v. Union Sanitary Dist., 946 F.2d 870 (Fed. Cir. 1991)).

Enclosed is a Petition for Extension of Time along with the required fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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